Gestational diabetes mellitus: diagnosis and outcome

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1 Introduction and aim of the thesis

GESTATIONAL DIABETES MELLITUS

Gestational diabetes mellitus (GDM) is one of the most common metabolic complications during pregnancy, and affects up to 14% of all pregnancies.[1,2] The prevalence of GDM is difficult to estimate as it largely depends on the population studied and the diagnostic criteria applied.[1,2] Nationwide data on the prevalence of GDM in the Netherlands are scarce, but the estimated prevalence varies between 2-5%.[3] Worldwide, the prevalence of GDM is still rising due to an increasing number of women with overweight and obesity during reproductive age and also the (recent) introduction of more stringent diagnostic criteria.[2,4-6] Approximately 14% to 20% of women of reproductive age are obese in developed countries.[7]

GDM is characterized as a medical condition in pregnancy in which women without previously diagnosed diabetes mellitus (DM) exhibit high blood glucose levels (hyperglycaemia) during pregnancy, classically developing during the second or third trimester. For women diagnosed with GDM in the first trimester of pregnancy, pre-existing DM or Maturity-Onset Diabetes of the Young (MODY) should be considered. In most of the women with GDM, blood glucose levels return to normal values after delivery.[8]

Physiology and pathophysiology

In pregnancy maternal metabolic changes occur to ensure continuous supply of nutrients for foetal development and growth.[9] Early pregnancy is characterized as an "anabolic state" and nutrients are stored in maternal tissue. In contrast, late pregnancy is more characterized as a "catabolic state".[10] During second and third trimester of pregnancy as the foetus starts to grow exponentially, its need for fuel (glucose) also rises exponentially. To facilitate glucose across the placenta there is an increase in maternal insulin resistance (decreased insulin sensitivity).[10,11] This decrease in the insulin-mediated glucose disposal in peripheral muscle cells of the mother, accommodates the increased foetal glucose demands.[11] The physiological factors partially responsible for the increase in insulin resistance are the combination of increased maternal adiposity and in the insulin-desensitizing effects of placental hormones, including human placental lactogen, progesterone, corticotrophin-releasing hormone, and estrogen.[11,12,13] To maintain normal glucose control during pregnancy, the pancreatic β-cells of the mother have to increase insulin secretion to meet the increased insulin requirements.[12,13]

The development of GDM occurs when the woman's pancreatic function fails to compensate for the increased resistance to insulin.[12] Studies have suggested that a majority of the women with GDM already have pancreatic β-cell dysfunction and/or chronic insulin resistance before pregnancy.[11,12,13]

PREGNANCY COMPLICATIONS

Comparable with pre-existent maternal DM in pregnancy, GDM is also associated with an increased risk of complications for both mother and child. These complications are attributed to the effects of uncontrolled hyperglycaemia in the second and third trimester of pregnancy. It has been demonstrated that there is a graded linear association between maternal blood glucose concentrations and the risk of adverse pregnancy outcomes.[14-16] Moreover, there is growing evidence of long-term health consequences for both mother and child.[17-21]

Short-term complications

The presence of GDM can adversely affect neonatal and maternal outcomes during pregnancy and childbirth. When GDM pregnancy remains untreated, the neonate is exposed to elevated blood glucose levels. Maternal insulin cannot cross the placental barrier, as a result the neonate increases its own insulin production, resulting in foetal hyperinsulinaemia.[22] The combination of hyperinsulinaemia and hyperglycaemia will lead to excessive foetal growth **(Fig. 1)**.[22,23] Excessive foetal growth is also called "macrosomia", and at delivery macrosomia is defined as a birth weight >4000 gram or "large for gestational age" (LGA), defined as a birth weight >90th percentile. Excessive foetal growth is one of the most common complications of GDM and can lead to an increased risk of birth injury (shoulder dystocia) and maternal morbidity from instrumental vaginal delivery or caesarean section.[22,23]

Other neonatal complications associated with GDM include neonatal hypoglycaemia, neonatal hyperbilirubinaemia (jaundice), preterm delivery, and admission to the neonatology department.[15,24-26] Additionally, GDM increases the maternal risk of hypertensive disorders during pregnancy like pregnancy-induced hypertension and preeclampsia.[15,25]

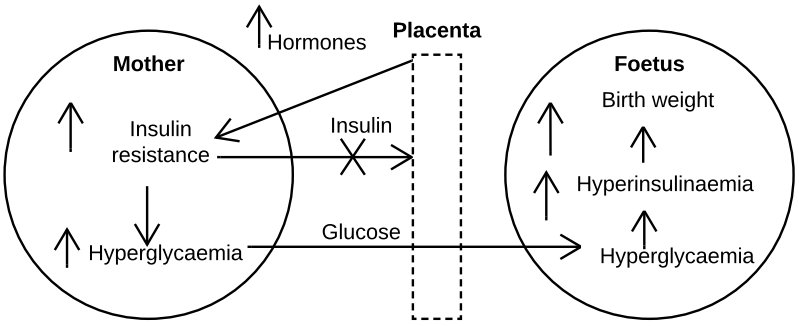

FIGURE 1. Pathophysiology of foetal macrosomia in GDM (Pedersen's hypothesis).

Long-term complications

Although in most of the women with GDM blood glucose levels return to normal values after delivery, GDM is a strong predictor to develop future impaired glucose tolerance and type 2 DM (T2DM). Epidemiological studies have demonstrated that the risk of developing T2DM may be as high as 50% in the first 5-10 years postpartum.[17,18] In addition, recent studies have suggested that women with a history of GDM also carry an increased risk for cardiovascular diseases.[27-29]

Several studies have indicated that children born to mothers with GDM also have an increased risk to develop obesity, metabolic syndrome, and T2DM.[19-21] However, this topic is still contradictory and awaiting confirmation.[30,31]

DETECTION AND TREATMENT

Intervention studies have clearly shown that GDM is a treatable condition and that adequate glucose control during pregnancy can effectively decrease pregnancy complications such as excessive foetal growth, shoulder dystocia, caesarean delivery, and hypertensive disorders.[32,33] National and international guidelines recommend to screen for GDM. However, there is no worldwide uniformly accepted and implemented guideline for screening and diagnosis of GDM.[34] In the Netherlands, the Dutch Society of Obstetrics and Gynaecology developed a guideline "Diabetes and Pregnancy" for the screening, diagnosis and treatment of GDM, which was implemented in 2010.[35] This guideline focuses on active screening and treatment policy provided by "usual care", where its diagnostic cut-off values are primarily based on the World Health Organization (WHO) criteria originating from 1999.[36] The latter largely differ from recent updates in diagnostic criteria by the International Association of Diabetes and Pregnancy Study Group (IADPSG) and WHO-2013 thresholds for diagnosis of GDM.[37,38]

Screening and diagnosis

GDM is seldomly recognized because of hyperglycaemic symptoms and is mostly diagnosed by a screening oral glucose tolerance test (OGTT). According to the Dutch national guideline, screening for GDM is recommended in women with one or more risk factors for GDM or signs suggestive of GDM (e.g. foetal macrosomia and/or polyhydramnios). Risk factors related to GDM are: having a pre-gestational body mass index ≥30 kg/m^2; having a previous infant weighing ≥4500 gram at birth or a birth weight >95th percentile; having a first degree relative with DM; having a history of GDM, (unexplained) intrauterine foetal death or polycystic ovary syndrome; and belonging to an ethnic risk group (South-Asian i.e. Hindu, Afro-Caribbean,

Middle-Eastern i.e. Moroccan and Egyptian). Pregnant women carrying at least one GDM risk factor should therefore be routinely screened with an OGTT between 24 and 28 weeks of gestation. Women with a history of GDM are screened between 16 and 18 weeks of gestation and between 24 to 28 weeks of gestation.[35]

The Dutch national guideline recommends the one-step screening strategy for GDM. The one-step screening strategy means the single use of a 75-g OGTT, whereby GDM is diagnosed on the basis of one abnormal value for either the fasting or the two-hour glucose levels. GDM is diagnosed when the fasting plasma glucose exceeds 7.0 mmol/l and/or 2-h glucose value ≥7.8 mmol/l after the 75-g glucose load.[35] The values of the diagnostic criteria are based on the old WHO-1999 consensus and have until now not been updated to the newest IADPSG/WHO-2013 criteria (75-g OGTT; fasting plasma glucose ≥5.1 mmol/l; and/or 1-h glucose value ≥10.0 mmol/l; and/or 2-h glucose value ≥8.5 mmol/l).[36-38]

Treatment

The main goal of treatment of GDM is to maintain adequate glucose levels during pregnancy. Lifestyle changes (healthy eating and exercise) are often sufficient to achieve adequate glucose control. Therefore, the first step of GDM treatment is nutritional advice by a dietician, which includes advice about carbohydrate distribution and carbohydrate intake. Moreover, women receive advice regarding self-monitoring of the blood glucose values by a diabetes specialist nurse. Treatment targets for GDM are a fasting plasma glucose level ≤5.3 mmol/l and/or one-hour postprandial plasma glucose level ≤7.8 mmol/l.[35] When dietary advice fails to maintain glycaemic control, insulin therapy is the second step in GDM treatment. To date, the use of insulin therapy is the medication of choice in GDM as recommended in most international guidelines, although there is debate whether oral blood glucose-lowering agents may have a place in the treatment. In the United Kingdom, metformin has already been incorporated into the "National Institute for Health and Care Excellence" (NICE) guideline.[39]

Glucose testing after pregnancy is very important to reduce the rising T2DM pandemic. In the Netherlands, women are advised to visit the general practitioner (GP) at six weeks after delivery and subsequently once a year for the next five years for follow-up glucose testing.[35,40] Moreover, the GP can motivate women to adopt and maintain a healthy lifestyle to prevent T2DM.

International guidelines

Although screening, diagnosis and treatment of GDM importantly reduce the risk connected to GDM, international guidelines on diagnostic cut-off values and treat-

ment vary and are predominantly the result of consensus instead of well-defined controlled outcome studies.

Chapter 2 provides a more extensive overview of the different diagnostic criteria and treatment modalities worldwide and the reasons for the discrepancies. In **Chapter 2** we describe both the current knowledge regarding GDM and the unmet needs of this condition. We review the diagnostic criteria, different treatment regimens available (including diet, insulin therapy and the use of oral blood glucose-lowering agents), and the long-term consequences of GDM.

AIM AND OUTLINE OF THE THESIS

The Dutch Society of Obstetrics and Gynaecology guideline "Diabetes and Pregnancy" for the screening and treatment of GDM, was implemented in 2010 and largely follows the older WHO-1999 diagnostic criteria. However, new insights regarding hyperglycaemia during pregnancy have been reported and this has led to a national and international debate regarding the diagnosis and treatment of GDM encouraged by the newer more stringent diagnostic criteria proposed by the IADPSG/WHO-2013. There is much uncertainty regarding the optimal glucose thresholds to define GDM.

Therefore, the aim of this thesis is to evaluate the current Dutch national guidelines for diagnosis and treatment of GDM i.e. what is the outcome of GDM pregnancies using this guideline? And what are consequences when the current diagnostic criteria of GDM are to be revised?

Outline of the thesis

This thesis comprises two parts. In the first part we evaluate the current Dutch national guidelines for diagnosis and treatment of GDM. In the second part we evaluate the pregnancy outcomes with respect to the new international diagnostic criteria for GDM compared with the current diagnostic thresholds.

In **Chapter 2** an overview of the different diagnostic criteria and treatment modalities worldwide is presented, and the unmet needs of this condition are outlined.

The first part consists of the **Chapters 3, 4, 5** and **6** and describes the outcomes of the current Dutch national guidelines for GDM. In **Chapter 3** we aimed to evaluate the neonatal and obstetric outcomes of pregnancies complicated by GDM after implementation of the 2010 Dutch Society of Obstetrics and Gynaecology "Diabetes and Pregnancy" guideline on screening and treatment. The pregnancy outcomes were compared between diet- and insulin treated women. In addition, we com-

pared the GDM outcomes with the general obstetric population in the northern region of the Netherlands. We hypothesized that women treated with insulin are more likely to have adverse pregnancy outcomes and deliver children with a higher birth weight, due to a greater difficulty to maintain glycaemic control. In **Chapter 4** we aimed to allow the recognition of a more "complex-care" group of insulin-treated women with GDM, but on the other hand a potential "low-risk" group of women treated with diet alone and likely to have good obstetric and/or neonatal outcomes. In **Chapter 5** we aimed to investigate the potential effect of thyroid function (measured in second trimester of pregnancy) on maternal and neonatal outcomes in women with GDM. We hypothesized that women with GDM and lower FT4 levels in the normal-range are more likely to have a higher weight gain during pregnancy and unfavourable pregnancy outcomes. In **Chapter 6** we aimed to evaluate the adherence to follow-up six-weeks postpartum visit in secondary care after GDM and glucose testing longer than 12-14 months after delivery and the years thereafter in primary care. In addition, we also examined by questionnaire the lifestyle of the women with a history of GDM including physical activity and diet.

The second part consists of **Chapters 7** and **8** and describes the pregnancy outcomes with respect to the new international diagnostic criteria for GDM compared with the current diagnostic thresholds. In **Chapter 7** we aimed to investigate the possible impact on GDM prevalence and pregnancy outcomes of applying the new WHO-2013 criteria instead of the older WHO-1999 criteria. Pregnancy outcomes were compared between a normal glucose tolerance control-group and different GDM classification groups. In **Chapter 8** we aimed to evaluate the maternal characteristics and pregnancy outcomes in two cohorts applying different diagnostic criteria for GDM i.e. WHO-2013 and WHO-1999. All women were treated according the Dutch national guideline. This study was in collaboration with Deventer Hospital. This hospital already implemented the new IADPSG/WHO-2013 thresholds for diagnosis of GDM in 2012.

Finally, **Chapter 9** provides a summary, general discussion, and future perspectives.

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